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### Testing differential susceptibility

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## Testing differential susceptibility: Plasticity genes, the social environment, and their interplay in adolescent response inhibition

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ORIGINAL INVESTIGATION

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## Testing differential susceptibility: Plasticity genes, the social environment, and their interplay in adolescent response inhibition

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### ABSTRACT

**Objectives:** Impaired inhibitory control is a key feature of attention-deficit/hyperactivity disorder (ADHD). We investigated gene–environment interaction (GxE) as a possible contributing factor to response inhibition variation in context of the differential susceptibility theory. This states individuals carrying plasticity gene variants will be more disadvantaged in negative, but more advantaged in positive environments.

**Methods:** Behavioural and neural measures of response inhibition were assessed during a Stop-signal task in participants with ( $N = 197$ ) and without ( $N = 295$ ) ADHD, from  $N = 278$  families (age  $M = 17.18$ ,  $SD = 3.65$ ). We examined GxE between candidate plasticity genes (*DAT1*, *5-HTT*, *DRD4*) and social environments (maternal expressed emotion, peer affiliation).

**Results:** A *DRD4*  $\times$  Positive peer affiliation interaction was found on the right fusiform gyrus (rFG) activation during successful inhibition. Further, *5-HTT* short allele carriers showed increased rFG activation during failed inhibitions. Maternal warmth and positive peer affiliation were positively associated with right inferior frontal cortex activation during successful inhibition. Deviant peer affiliation was positively related to the error rate.

**Conclusions:** While a pattern of differential genetic susceptibility was found, more clarity on the role of the FG during response inhibition is warranted before firm conclusions can be made. Positive and negative social environments were related to inhibitory control. This extends previous research emphasizing adverse environments.

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### KEYWORDS

ADHD; response inhibition; gene–environment interaction; social environment; functional MRI


## Introduction

The ability to control oneself by suppressing or altering intended actions that are no longer required or appropriate is referred to as response inhibition (Diamond 2013). Response inhibition is considered one of the three core executive functions, the others being working memory and cognitive flexibility (Miyake et al. 2000). Through inhibition-related processes top-down cognitive control is exerted, thereby regulating attention, behaviour, thoughts and emotions (Diamond 2013). Impaired inhibitory control has been implicated


in several neuropsychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder and substance-related disorders (Lipszyc & Schachar 2010; Warren et al. 2013; Smith et al. 2014; van Velzen et al. 2014). Twin studies show that the aetiology of response inhibition is best explained by a combination of genetic and non-shared environmental factors (Friedman et al. 2008; Schachar et al. 2011), with moderate heritability estimates (0.31–0.50) (Friedman et al. 2008; Schachar et al. 2011; Crosbie et al. 2013). Studying the effects of genes,

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environmental influences and their interaction could provide more insight into interindividual differences in response inhibition.

Gene variants in the dopamine and serotonin neurotransmission system have been reported to contribute to interindividual differences in response inhibition and its neural correlates (Swanson et al. 2000; Cornish et al. 2005; Stoltenberg et al. 2006; Congdon et al. 2008; Baehne et al. 2009; Congdon et al. 2009; Kramer et al. 2009; Braet et al. 2011; Cummins et al. 2012; Filbey et al. 2012; Landro et al. 2014; Mulligan et al. 2014). Two variable number tandem repeat (VNTR) polymorphisms, one found in the 3'untranslated region (3'UTR) of the dopamine transporter gene (*SLC6A3/DAT1*) and the other in the exon 3 of the dopamine receptor D4 gene (*DRD4*), have been associated with decreased response inhibition performance (Cornish et al. 2005; Congdon et al. 2008; Congdon et al. 2009; Filbey et al. 2012; Mulligan et al. 2014). Carriers of two *DAT1* 10-repeat alleles or the *DRD4* 7-repeat performed worse on response inhibition tasks, as indicated by slower verbal responses (Cornish et al. 2005), longer motor response latencies (Congdon et al. 2008) and less successful inhibited motor responses (Filbey et al. 2012). In addition, compared to individuals without the *DAT1* 10/10 genotype or *DRD4* 7-repeat reduced activation during inhibition was found in prefrontal areas such as the orbital and inferior frontal cortex, anterior cingulate gyrus, premotor cortex and pre-supplementary motor area; as well as in temporal and posterior areas and the subthalamic nucleus (Congdon et al. 2009; Filbey et al. 2012; Mulligan et al. 2014). Note that conflicting findings have been reported as well, as slower inhibition was reported in non-carriers of the 7-repeat, as was increased response accuracy for 7-repeat homozygotes (Swanson et al. 2000; Kramer et al. 2009). Furthermore, increased activation during response inhibition, but decreased activation during error response was found in carriers of the *DAT1* 10/10 genotype (Braet et al. 2011). Null-findings have also been reported (Langley et al. 2004; Rommelse et al. 2008; Colzato et al. 2010; Heinz et al. 2013). Carriers of the short allele of the serotonin transporter (*SLC6A4/5-HTT*) *HTTLPR* polymorphism were found to exhibit worse inhibitory control than those without this allele (Landro et al. 2014). However, two smaller previous studies did not find an association between *HTTLPR* and inhibitory control (Clark et al. 2005; Druke et al. 2010).

Importantly, the above-mentioned studies manifest large variation in design and methods, i.e., in the included sample (e.g., clinical vs. healthy individuals,

children vs. adults) and type of task used (e.g., stop-signal task vs. go-no-go task). Moreover, only few studies used a sample size  $> N = 100$  (Langley et al. 2004; Congdon et al. 2008; Colzato et al. 2010; Heinz et al. 2013). These factors are likely to contribute to the inconsistent results.

Studies investigating environmental influences on response inhibition have been less common. Adverse early family environment in children (Lewis et al. 2007; Tibu et al. 2016) and chronic stress in animal studies (Beydoun and Saftlas 2008; Mika et al. 2012) have been associated with poorer inhibitory control, while two other studies failed to find effects of psychosocial adversity, including marital conflict, parental psychopathology and stressful life events (Van den Bergh et al. 2005; Nigg et al. 2007). Negative environmental experiences not only seem to influence behaviour but also the neural correlates of response inhibition. Childhood maltreatment has been associated with altered inhibitory control network connectivity (Elton et al. 2014), which was related to poorer response inhibition in males, but with opposite effects in females. Moreover, prenatal exposure to tobacco smoke has been associated with lower neural activation during response inhibition (Holz et al. 2014). Further support for environmental effects comes from studies into behavioural impulsivity, which may be considered a consequence of impaired response inhibition (Diamond 2013). Studies on behavioural impulsivity as measured through questionnaires or interviews have demonstrated greater impulsivity in children exposed to maternal smoking and alcohol use during pregnancy (Polanska et al. 2012), maternal stress (Beydoun & Saftlas 2008) and marital conflict (Counts et al. 2005). Together, most findings suggest adverse environments are associated with worse inhibitory control, although additional studies are needed to clarify inconsistent results.

One suggested possible mechanism through which adverse environments could lead to less adequate inhibitory control is dysregulated neuroendocrine functioning (Lewis et al. 2007). For example, dysregulated cortisol levels can have a negative effect on the brain, through processes such as neuronal loss, delays in myelination and the inhibition of neurogenesis (Lewis et al. 2007; Lupien et al. 2009). However, the specific effects of adverse environments on the brain may depend on a person's genotype. Indeed, studies on behavioural impulsivity have shown that genetic and environmental factors may interact (gene-environment interaction, GxE) (Laucht et al. 2007; Wagner et al. 2009; Willcutt et al. 2010; Nishikawa et al. 2012; van der Meer et al. 2014), though GxE effects on

behavioural and neural measures of response inhibition have not been investigated previously. There are different theoretical models to explain how and why genes moderate environmental experiences. Most commonly applied is the diathesis-stress or vulnerability model (Zubin & Spring 1977; Monroe & Simons 1991), in which genes are viewed as vulnerability or risk factors that moderate the effects of adverse environments, but have no effect in beneficial environments. Recently gaining increased attention in research, the differential susceptibility theory extends this view by positing the existence of plasticity genes, which moderate the effects of both negative and positive environmental factors (Belsky 1997; Belsky et al. 2009; Ellis et al. 2011). For example, for *DAT1*, *DRD4* and *5-HTT*, the most investigated candidate plasticity genes, it has been shown that individuals carrying specific variants of these genes display the worst outcome when exposed to negative environments, but also benefit most from positive environments (Bakermans-Kranenburg & van IJzendoorn 2011; Beaver & Belsky 2012; van IJzendoorn et al. 2012; Belsky & Pluess 2013). As these genes have also been implicated in behavioural and neural response inhibition (Cornish et al. 2005; Congdon et al. 2008, 2009; Braet et al. 2011; Filbey et al. 2012; Landro et al. 2014; Mulligan et al. 2014), and given the mixed results found for both genetic and environmental influences on response inhibition, it is quite plausible that these genes act to moderate the effect of positive and negative environments on response inhibition.

The current study used the differential susceptibility model to examine GxE effects on interindividual differences in response inhibition. We investigated behavioural and neural correlates of response inhibition in children, adolescents and young adults with and without ADHD. Impaired response inhibition is central to theoretical models of ADHD (Barkley 1997; Oosterlaan et al. 1998; Alderson et al. 2007; Lipszyc & Schachar 2010). For example, it has been argued that response inhibition is a central deficit of ADHD that may have downstream effects on executive functions, including working memory, self-regulation, internalization of speech and reconstitution (Barkley 1997; Oosterlaan et al. 1998; Alderson et al. 2007). On average, individuals with ADHD inhibit their responses more slowly than controls, with a meta-analysis reporting a medium effect-size of  $g = 0.62$  (Lipszyc & Schachar 2010). In addition, a large community study showed that ADHD symptoms in children and adolescents are associated with worse response inhibition and slower response inhibition latency (stop-signal reaction times, SSRT; Crosbie et al. 2013). However, not all individuals with

ADHD show impaired response inhibition (Nigg et al. 2005; Sjowall et al. 2013). For example, 60–80% of patients with ADHD have an overlapping SSRT with typical developing controls (Lipszyc & Schachar 2010; van Rooij et al. 2015b). Furthermore, deficits in response inhibition are not only found in individuals with an ADHD diagnosis or ADHD symptoms, but can be found in healthy controls as well (Fair et al. 2012). Thus, great individual variation in response inhibition can be found in both individuals with and without ADHD.

Event-related functional magnetic resonance imaging (MRI) was used to investigate the neural responses during the stop-signal task (SST; Logan et al. 1984; Hart et al. 2013). Using this task, our group has shown worse performance and decreased activations during successful and failed inhibition in adolescents with ADHD compared with controls (van Rooij et al. 2015b). As susceptibility factors, we included the short allele of *HTTLPR*, the 7-repeat allele of *DRD4* and homozygosity for the 10-repeat allele of *DAT1*. Furthermore, we extend previous research on inhibitory control that has thus far focused primarily on adverse environments by including both positive and negative sides of maternal expressed emotions (EE; warmth and criticism) and peer affiliation (positive and deviant) as a proxy of the social environment. The social environment (i.e., interactions with parents and peers) plays an important role in the development of self-regulation (Farley & Kim-Spoon 2014), which includes response inhibition (Diamond 2013). Positive parenting and high-quality relationships with peers promote optimal self-regulation skills (Lewis et al. 2007; Farley & Kim-Spoon 2014). Based on the findings of lower behavioural and neural inhibition in adolescents with ADHD, we hypothesized that, if differential susceptibility theory applies, one would expect participants carrying plasticity variants to show the most positive outcomes (e.g., improved inhibitory control) when exposed to positive EE or peer affiliation *and* the most negative outcomes (e.g., less inhibitory control) when faced with negative EE or peer affiliation.

## Methods and Materials

### Participants

Participants were selected from a follow-up (2009–2012) of the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study, performed between 2003 and 2006 (see Brookes et al. 2006). At first enrolment in IMAGE, families with at least one child with combined type ADHD and at least one



biological sibling (regardless of ADHD diagnosis) were recruited, in addition to control families with at least one (unaffected) child and no formal or suspected ADHD diagnosis in first-degree family members. Inclusion criteria for children were an age between 5 and 19 years, European Caucasian descent, IQ  $\geq 70$ , and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders or known genetic disorders (such as fragile X syndrome or Down syndrome). All families were reinvited for a follow-up assessment with a mean follow-up period of 5.9 years (SD = 0.74). A comprehensive assessment protocol was administered (see von Rhein et al. 2015; [www.neuroimage.nl](http://www.neuroimage.nl)), encompassing behavioural questionnaires, a diagnostic interview (e.g., of ADHD, oppositional defiance disorder – ODD, conduct disorder – CD), and several neurocognitive measures from all family members, and an extensive MRI scanning protocol in participating children. Participants were asked to withhold use of psychoactive drugs for 48 h before measurement. To determine ADHD diagnoses at the follow-up measurement, a standardized algorithm was applied containing a combination of questionnaires and a semi-structured diagnostic interview. For a detailed description of the diagnostic procedure see (von Rhein et al. 2015). The study was approved by the local ethics committees, and informed consent was signed by all participants and their parents in case participants were below 18 (only parents provided consent for participants under 12 years of age).

In the current analyses, participants were included when the SST was administered and information was available on EE or peer affiliation:  $N = 197$  participants with ADHD,  $N = 49$  with subthreshold ADHD (i.e., elevated symptoms of ADHD without meeting the full criteria for an ADHD diagnosis), and  $N = 246$  without ADHD, from  $N = 278$  families. A flowchart of participant inclusion can be found in the Supplementary Information (SI), Figure S1, available online. Sample size depended in particular on the availability of EE ( $N = 221$ ) and peer affiliation ( $N = 478$ ) as EE could only be assessed when the diagnostic interview was administered. This led to an unequal distribution of participants with or without an ADHD diagnosis in the EE ( $N = 173$  with ADHD,  $N = 27$  with subthreshold ADHD,  $N = 21$  without ADHD) vs. peer affiliation selection ( $N = 186$  with ADHD,  $N = 47$  with subthreshold ADHD,  $N = 245$  without ADHD). Therefore, participant characteristics in Table 1 displayed separately for EE and peer affiliation. Exact numbers of participants with an ADHD diagnosis separate for the behavioural and neural measures, and per gene selection are shown in Figure S1 (Supplementary material, available online).

## Measures

### Parental EE

Parental EE was assessed during the semi-structured diagnostic interview, using codings derived from the Camberwell Family Interview (Brown 1966). Only ratings of mothers were used in our study, as the data of fathers were far less complete. Warmth was assessed by the tone of voice, spontaneity, sympathy and/or empathy toward the child (range 0–3). Criticism was assessed by statements which criticized or found fault with the child based on tone of voice and critical phrases (range 0–4) (Richards et al. 2014; Sonuga-Barke et al. 2009). The inter-rater reliability has been found to be adequate using similar codings for warmth and criticism (range 0.78–0.91 and 0.79–0.86, respectively (Schachar et al. 1987). During the first measurement wave (the IMAGE study), an average agreement percentage of 96.6% (range 78.6–100) and a mean Kappa coefficient of 0.88 (range 0.71–1.00) were obtained across all sites for the total PACS-interview, including the EE ratings (Chen and Taylor 2006).

### Peer affiliation

Peer affiliation was measured with the Friends Inventory (Walden et al. 2004). Participants assessed their peers' behaviour on 18 items rated on a four-point Likert scale (e.g., "My friends get good grades", "My friends break the rules"; range 1 = "None of my friends are like that" to 4 = "All of my friends are like that"). Scores were summed to yield either a positive or deviant peer affiliation score (each nine items). Both have demonstrated good internal consistency reliability (range 0.78–.92; Burt et al. 2009; Hicks et al. 2009; Burt & Klump 2014) and a mean inter-rater reliability of 0.71 has been reported between teacher and self-reports (Hicks et al. 2009). Several studies have used peer affiliation as a proxy of the social environment (see e.g., Gifford-Smith et al. 2005; Vitaro et al. 2011; Fabes et al. 2012).

### ADHD severity

The Dutch Conners' Parent Rating Scale (CPRS-R:L) was used to assess ADHD severity (i.e., the raw scores of scale N – DSM-IV: total) (Conners et al. 1998). We used the CPRS-R:L as it was assessed in all participants (regardless of diagnostic status). Moreover, using a continuous measure of ADHD severity allowed us to retain as much information as possible, including the variation of scores among unaffected participants.

**Table 1.** Participant characteristics.

	Expressed emotions selection			Peer affiliation selection		
	N	M	SD	N	M	SD
Number of families	165			273		
ADHD diagnosis	173	78%		186	39%	
Inattentive type	81	37%		88	18%	
Hyperactive-impulsive type	21	10%		27	56%	
Combined type	71	32%		71	15%	
Subthreshold	27	12%		47	10%	
Unaffected	21	10%		245	51%	
ADHD severity (CPRS)	219	20.42	11.54	469	11.89	11.86
ODD diagnosis	59	27%		57	12%	
CD diagnosis	136	6%		13	3%	
History of stimulant use	159	72%		170	36%	
Male	145	66%		263	55%	
Collection site (Amsterdam)	88	40%		234	49%	
Age	221	16.85	3.21	478	17.22	3.68
Estimated IQ	220	96.30	15.71	475	101.53	16.00
Maternal warmth/positive peer affiliation	221	1.56	0.87	470	22.73	3.57
Maternal criticism/deviant peer affiliation	221	1.69	0.89	478	14.61	4.31
SSRT (ms)	221	270.56	62.88	478	264.90	58.42
Variability (ms)	221	112.24	40.49	478	97.58	39.17
Errors (N)	221	6.60	8.07	478	5.22	7.10
Successful stop rACC	204	21.23	27.23	451	21.92	26.55
Failed stop rACC	204	37.18	28.87	451	38.37	28.41
Successful stop rIFG	204	42.27	32.83	451	42.58	31.74
Failed stop rIFG	204	54.84	32.95	451	56.67	33.07
Successful stop rFG	203	6.04	16.16	450	6.86	16.68
Failed stop rFG	203	10.58	17.14	450	9.80	16.34
DAT1	206			452		
9-repeat present	81 <sup>b</sup>	39%		174 <sup>c</sup>	38%	
9-repeat absent <sup>a</sup>	125	61%		278	62%	
5-HTT	216			468		
Short allele present	132 <sup>d</sup>	61%		287 <sup>e</sup>	61%	
Short allele absent	84	39%		181	39%	
DRD4	217			468		
7-repeat present	77	36%		173	37%	
7-repeat absent	140	65%		295	63%	

CPRS, Conners' Parent Rating Scale; rACC, right anterior cingulate cortex/supplementary motor area; rIFG, right inferior prefrontal cortex/insula; rFG, right fusiform gyrus. ODD and CD diagnoses were based on K-SADS structured psychiatric interviews (Kaufman et al. 1997). Estimated IQ was based on two subtests of the WISC/WAIS-III: Vocabulary and Block Design (Wechsler 2000, 2002).

<sup>a</sup>10/10 genotype.

<sup>b</sup>N = 15 (7%) with two 9-repeats.

<sup>c</sup>N = 28 (6%) with two 9-repeats.

<sup>d</sup>N = 34 (16%) with two short alleles.

<sup>e</sup>N = 68 (15%) with two short alleles.

## SST

An adapted version of the SST (Logan et al. 1984) was used to measure response inhibition (van Rooij et al. 2015b). Participants were instructed to respond as quickly as possible to a Go signal, unless the Go signal was followed by a Stop signal after a short interval, in which case they were instructed to withhold their response. The delay between Go and Stop signals was adapted on-line, leading to successful inhibition in average 50% of the Stop trials (see SI). The task started with a practice block of Go trials and a practice block of mixed Go and Stop trials, followed by four blocks of 60 trials (48 Go and 12 Stop trials), separated by 1-min intervals.

As behavioural measures of response inhibition, we included the SSRT, which reflects the time necessary for subjects to successfully inhibit their response; the

number of omission and commission errors on Go-trials (*errors*); and the intra-individual *variability* (standard deviation, SD, divided by mean reaction time, MRT, over all Go trials) (de Zeeuw et al. 2008). Neural activation was assessed using the blood oxygen level-dependent (BOLD) response during performance on the SST. After preprocessing of MRI data (details on image acquisition and preprocessing can be found in the SI), we calculated first-level contrasts for successful and failed Stops (contrast of parameter estimates of successful or failed Stops vs. Go trials; i.e., Go trial activity was used as an implicit baseline to isolate activation unique to the successful and failed Stop trials). For these two contrasts the mean BOLD response was extracted from five a-priori defined regions of interest (ROIs): the right anterior cingulate cortex (rACC)/supplementary motor area (SMA), right inferior frontal

cortex (rIFC)/insula, right thalamus, left caudate head and right fusiform gyrus (rFG). All are considered core regions of the inhibition system (Hart et al. 2013). The ROIs were defined on the basis of Talairach coordinates (ACC/SMA: 4,10,48; IFC/insula: 36,18,8; thalamus: 4,-16,4; caudate: -16,-8,22; FG: 26,-58,-8; transformed to MNI using tal2icbm tools, see <http://www.brainmap.org/icbm2tal/>) derived from a meta-analysis (Hart et al. 2013), with a 6-mm sphere around the coordinates (Hedden & Gabrieli 2010). As described in the SI and shown in Figure S2 (available online), nearly all ROIs showed task activation sensitive to response inhibition. Exceptions were the right thalamus and left caudate, which did not fall within the task activation maps and were therefore excluded from further analyses.

### Genotyping

For the IMAGE sample (parents and children), DNA was extracted from blood samples or immortalized cell lines at Rutgers University Cell and DNA Repository, NJ, USA. The genetic variants in *DAT1*, *5-HTT* and *DRD4*, were genotyped by the IMAGE consortium (Brookes et al. 2006; Xu et al. 2008). Standard PCR protocols were used for all VNTR markers and amplified products were visualized on 2% agarose under UV light. Additional NeuroIMAGE samples were collected in the form of a saliva sample using Oragene kits (DNA-Genotek; see [www.neuroimage.nl](http://www.neuroimage.nl)). VNTRs were genotyped using standard PCR protocols. After the PCR, fragment length analysis was performed on the ABI prism 3730 Genetic Analyser (Applied Biosystems, Nieuwekerk a/d IJssel, The Netherlands) and results were analyzed with GeneMapper® Software, version 4.0 (Applied Biosystems). No deviations from Hardy–Weinberg Equilibrium were found (*DAT1*  $P=0.78$ , *5-HTT*  $P=0.13$ , *DRD4*  $P=0.15$ ). For each gene, participants were divided into groups based on the presence or absence of the candidate plasticity alleles (i.e., homozygosity for the 10-repeat allele of the *DAT1* 3'UTR VNTR, the short allele of *HTTLPR*, the 7-repeat of the *DRD4* exon 3 VNTR).

### Data Analyses

Pearson and Spearman correlations tested for gene–environment correlations between maternal or adolescent candidate plasticity genes and the environmental predictors (Belsky & Pluess 2009; Knafo & Jaffee 2013). Linear mixed-model analyses investigated the effects of EE, peer affiliation, genotype and GxE interactions on each inhibition outcome measure. Models were run with and without the interaction

term separately. To correct for familial dependency (i.e., a number of participants belonged to the same families), we estimated a random intercept for family in each model. Age, sex and collection site were included as confounders. Separate models were run for each environmental predictor: warmth, criticism, positive and deviant peer affiliation, as for both EE and peer affiliation positive and negative scales were not sufficiently correlated to create one scale ( $r = -0.55$  and  $r = -0.16$ , respectively). Separate models were run for each potential plasticity gene (*DAT1*, *5-HTT*, *DRD4*) as well. All environmental predictors were centred around the mean and the inhibition outcome measures were normalized using Van der Waerden's formula.

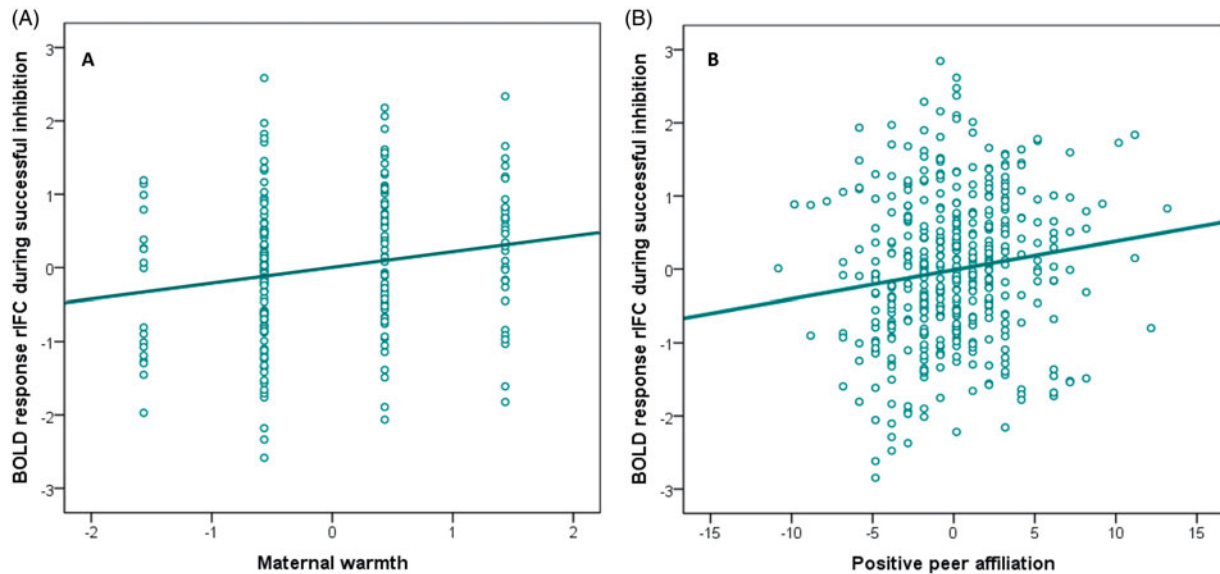
A multiple comparisons correction was employed which adjusts for correlated outcomes based on the effective number of independent tests ( $M_{\text{eff}}$ ) (Li & Ji 2005). The  $M_{\text{eff}}$  was derived from the Eigenvalues of a correlation matrix between the outcome measures adjusted for covariates (age, sex and collection site), separate for the behavioural ( $M_{\text{eff}}=3$ , adjusted  $P$  value threshold:  $P=0.05/3=0.017$ ) and neural data ( $M_{\text{eff}}=5$ , adjusted  $P$  value threshold:  $P=0.05/5=0.010$ ). Regions of Significance (RoS) and simple slope tests were performed with an online application designed for probing interactions in differential susceptibility research (<http://www.yourpersonality.net/interaction/>, see Roisman et al. 2012).

Sensitivity analyses were performed when significant effects were found (i.e., those that survived the multiple correction threshold). First, to investigate the role of ADHD severity, analyses were rerun now including main and interaction effects with ADHD severity. Furthermore, separate sensitivity analyses were performed to check whether significant effects were present in participants while controlling for nonlinear effects of age (age<sup>2</sup>), medication history, estimated IQ and comorbid ODD or CD diagnosis. All analyses were performed with the Statistical Package for the Social Sciences, version 20.0.

### Results

Testing for the presence of gene–environment correlations (rGE) revealed one significant association between adolescent *DAT1* genotype and maternal criticism ( $r=0.16$ ,  $P=0.019$ ; see SI, Table S1). Considering the small size of this association, there was no reason to believe it may have biased possible GxE effects. In what follows, only results that survived correction for multiple testing are discussed. Nominally significant





**Figure 1.** (A) Association between maternal warmth and the BOLD response in the rIFC during successful inhibition ( $B = 0.23$ ,  $P = 0.003$ ; normal score [0] = BOLD signal change 42.54). (B) Association between positive peer affiliation and the BOLD response in the rIFC during successful inhibition ( $B = 0.03$ ,  $P = 0.010$ ; normal score [0] = BOLD signal change 41.57).

effects can be found in Supplemental Tables S2, S3, S4 and S5, available online.

### Maternal EE

No significant GxE effects were found when investigating effects of maternal EE on any of the behavioural inhibition measures (Table S3, available online). However, maternal warmth was positively associated with the BOLD response in the right IFC during successful stops ( $B = 0.23$ ,  $P = 0.003$ ; see Figure 1 and Table S4).

### Peer Affiliation

For peer affiliation no significant GxE effects were found when investigating the behavioural inhibition measures either (Table S3). However, positive and deviant peer affiliation were significantly associated with the number of errors ( $B = -0.03$ ,  $P = 0.014$ ;  $B = 0.03$ ,  $P = 0.009$ , respectively, Table S2). In addition, positive peer affiliation was also positively associated with the BOLD response in the right IFC during successful stops ( $B = 0.03$ ,  $P = 0.010$  see Figure 1 and Table S4). Finally, a significant interaction between *DRD4* and positive peer affiliation was found on the BOLD response in the rFG during successful inhibitions ( $B = -0.07$ ,  $P = 0.006$ ; Table S5). As can be seen in Figure 2, carriers of the 7-repeat allele showed less activation when scoring higher on positive peer affiliation (simple slope  $P = 0.004$ ), while carriers

without the 7-repeat showed no association (simple slope  $P = 0.443$ ).

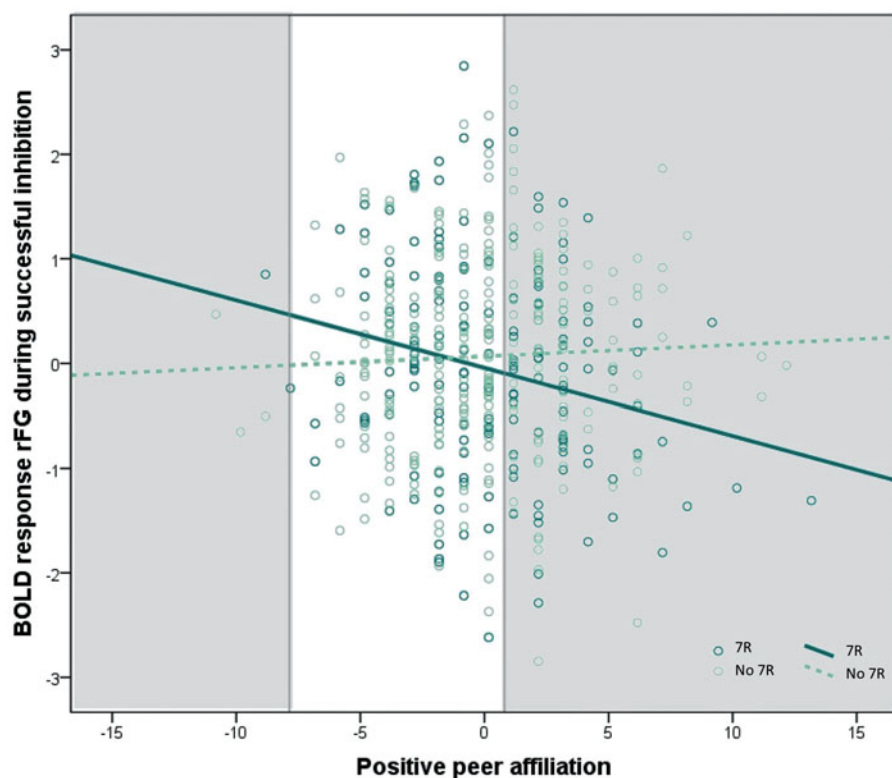
### Main genetic effects

A main effect of *5-HTT* was found on the BOLD response in the rFG during failed inhibitions. Carriers of the *HTTLPR* short allele showed more activation compared with carriers of two long alleles ( $B = 0.28$ ,  $P = 0.003$ ; see Figure 3 and Table S4). No further main gene effects were found.

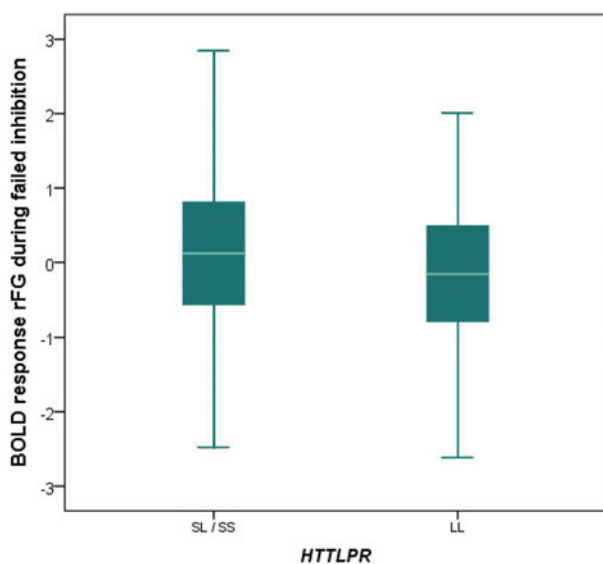
### Sensitivity Analyses

To investigate the possible role of ADHD on the above described significant effects, sensitivity analyses were run with ADHD severity as a moderator. For maternal EE, no significant interactions with ADHD were found. However, a significant interaction between ADHD severity and positive peer affiliation was found on IFC activation during successful stops ( $P = 0.001$ ). Only participants scoring low on ADHD severity showed a positive association between the BOLD response in the IFC and positive peer affiliation ( $P = 0.001$ ), while participants with high ADHD severity did not ( $P = 0.626$ ). No further significant two- or three-way interactions were found (all  $P$  values  $\geq 0.047$ ), nor did including a main effect of ADHD severity change the remaining significant effects.

When we accounted for nonlinear age effects, IQ, ODD, CD and medication history by rerunning analyses



**Figure 2.** Interaction between *DRD4* and positive peer affiliation on the BOLD response in the rFG during successful inhibition ( $B = -0.07$ ,  $P = 0.006$ ; normal score [0] = BOLD signal change 8.61). The shaded areas indicate the RoS, lower threshold:  $X = -7.86$ ; upper threshold:  $X = 0.93$ .



**Figure 3.** Association between *5-HTT* and the BOLD response in the rFG during failed inhibition ( $B = 0.28$ ,  $P = 0.003$ ; normal score [0] = BOLD signal change 8.61).

with these measures in the model, the significant effects of maternal warmth and deviant peer affiliation did not change. Exceptions were the effect of positive peer affiliation on the number of errors, which was no

longer significant when IQ ( $P = 0.086$ ) or medication history ( $P = 0.171$ ) were included, and the effect of positive peer affiliation on IFC activation, which was no longer significant when medication use was included ( $P = 0.058$ ).

## Discussion

We investigated the applicability of the differential susceptibility theory by studying GxE effects on behavioural and neural correlates of response inhibition. A GxE effect was found between *DRD4* and positive peer affiliation on the BOLD response during successful inhibitions in the rFG. In addition, a main effect of *5-HTT* was found on the BOLD response in the rFG during failed inhibitions. Furthermore, both maternal warmth and positive peer affiliation were positively associated with the BOLD response in the right IFC during successful inhibition. Post hoc results indicated that the latter association with peer affiliation was driven by participants scoring low on ADHD severity. Finally, we found that deviant peer affiliation was positively related to the number of errors made during task performance. To the authors' knowledge this is the first study to report GxE and positive

environmental associations with response inhibition-related neural activation.

The interaction between *DRD4* and positive peer affiliation revealed a negative association between positive peer affiliation and the rFG BOLD response during successful inhibition for 7-repeat carriers only. On the one hand, this pattern appears consistent with differential genetic susceptibility (Belsky et al. 2009). That is, only carriers of the candidate susceptibility variant showed a differential association between the environment and neural activation; with higher activation when exposed to low, but lower activation when exposed to high positive peer affiliation compared to individuals without the 7-repeat allele. On the other hand, based on previous associations of reduced neural activation during successful inhibition in individuals with ADHD – including the rFG (Hart et al. 2013) – we had hypothesized that *reduced* activation would be related to worse outcome and *increased* activation to positive outcome. When viewed this way, the negative correlation with positive peer affiliation (i.e., worse outcome associated with a positive environment) is opposite to what one would expect. Indeed, for both maternal warmth and positive peer affiliation we found a *positive* correlation with the right IFC activation. Consistent with the latter findings, a previous study demonstrated decreased IFC activation when exposed to negative environmental influences (Holz et al. 2014).

Nonetheless, the IFC and FG might be involved in different aspects of inhibition. While the IFC has received ample attention regarding its role in inhibition (e.g., as a brake, Aron et al. 2014; or related to saliency detection and initiation of a broader control network, Hampshire 2015), the FG has not. Studies that have focused on the FG during response inhibition suggest it is involved with the visual processing of the Stop cues. Thus, despite associations between decreased activation and ADHD, decreased neural activation in the FG might not necessarily reflect negative outcome. However, the lack of association with behavioural inhibition measures, makes it difficult to differentiate between higher activation as reflecting more attention to the inhibition cue, a stronger reaction to the inhibition cue or increased effort to inhibit (Hampshire 2015; Hampshire et al. 2010). In all, although our findings appear consistent with differential susceptibility, it is premature to make firm conclusions until we have a better understanding of what the neural activation in the FG during response inhibition reflects.

Possibly, the increased activation found in *DRD4* 7-repeat carriers when exposed to low positive peer affiliation (and vice versa) is the result of increased dopamine levels, as the 7-repeat is associated with

increased dopamine availability (Congdon & Canli 2008). Moreover, negative social environments have been related to increased dopamine levels in animal studies as well (Hall & Perona 2012). A similar mechanism might explain our finding that carriers of *HTTLPR* short allele showed increased activation in the right fusiform gyrus during failed inhibitions, as both dopamine and serotonin neurotransmission are considered relevant for cognitive control (Cools et al. 2011). The *HTTLPR* short allele has been associated with increased serotonin availability (Lesch et al. 1996). Our results are in line with the increased activation found in *HTTLPR* short allele carriers (compared to long allele carriers) during failed inhibitions in posterior nodes, including the cerebellum and cingulate cortex, in adolescents with and without ADHD by our group (van Rooij et al. 2015a). Although in that study decreased activations were found in frontal nodes of response inhibition during successful inhibitions for short allele carriers as well, leading to the suggestion of compensatory neural activations in the posterior areas for carriers of the SS genotype (van Rooij et al. 2015a).

Although the majority of studies have focused specifically on detrimental effects of adverse environments on inhibitory control, the importance of positive parental and peer influences becomes apparent when focusing on self-regulation literature. Response inhibition forms an important part of self-regulation (Diamond 2013). Self-regulation develops through complex interactions between a child and his or her social environment, i.e., parents at first and later peers as well (Farley & Kim-Spoon 2014). Positive parenting and high-quality relationships with peers promote optimal self-regulation skills (Farley & Kim-Spoon 2014; Lewis et al. 2007). Thus, in agreement with studies on self-regulation, the associations of maternal warmth and peer affiliation with IFC and FG responses during successful inhibition indicate the importance of positive environmental influences when investigating brain responses related to self-control.

The association between positive peer affiliation and IFC activation was moderated by ADHD severity; only participants scoring low on ADHD severity showed the observed positive association. Previous studies have shown that individuals with ADHD show lower IFC activation during successful inhibition than healthy controls (Hart et al. 2013). Possibly, the neural activation in adolescents scoring high on ADHD severity differs in such a magnitude that this overshadows potential effects of peer influences. Although speculative, the finding that the association with maternal warmth was present regardless of ADHD severity, while the association with peer

affiliation was not, could suggest parental influences are more important for inhibition-related brain processes of adolescents with ADHD when compared to peer influences. Additional studies focusing on the effects of parenting and peer influences on neural correlates of inhibition are warranted.

On the behavioural level we found that participants scoring high on deviant peer affiliation made more errors. Initially, an association was found with positive peer affiliation as well; however, sensitivity analyses indicated reduced effects when IQ or medication use were included. Whether or not to correct for IQ when investigating neurocognitive function is the subject of ongoing debate (Dennis et al. 2009). Because adequate task performance is intertwined with IQ and, similarly, medication is prescribed to enhance behavioural functioning, including these measures as covariates might lead to overcorrection. The findings do suggest, however, a stronger effect of deviant than positive peer affiliation, as the former association survived our sensitivity analyses. Our results agree with previous studies reporting negative associations between adverse (early) family environments or stress and inhibitory control or impulsivity (Counts et al. 2005; Lewis et al. 2007; Beydoun & Saftlas 2008; Polanska et al. 2012). However, two studies found no effects of psychosocial adversity or maternal anxiety on the estimated speed of inhibition (SSRT) (Van den Bergh et al. 2005; Nigg et al. 2007), which is consistent with the absence of SSRT associations in our results. The effects of deviant and positive peer affiliation on errors rather than the SSRT, here, indicate that environmental factors may influence more general attentional processes involved in the tasks, rather than (behavioural) response inhibition specifically (Bekker et al. 2005; Overtoom et al. 2009).

This study should be viewed in light of a number of strengths and limitations. Strengths were the use of a well-characterized sample, inclusion of both positive and negative environments, with both parental and peer influences assessed, and the analysis of both behavioural and neural measures of response inhibition. A limitation was that not all participants had an EE measurement. This led to loss of power, unequal numbers and an unequal distribution of ADHD and controls in the EE vs. peer affiliation analyses. However, sensitivity analyses with a continuous measure of ADHD severity available in participants with and without ADHD suggested that the unequal distribution had not biased our results. Furthermore, as discussed above, our study design was cross-sectional, therefore no conclusions can be drawn on causality. For example, it could be that rIFC activation causes adolescents to attract or affiliate with more “positive” peers. Future studies with longitudinal designs are

needed to establish a direction of causality. Finally, although we chose three a-priori ROIs considered to be main nodes of the inhibition-network (Hart et al. 2013), there are several other brain regions relevant for response inhibition that are worth further investigation (e.g., the left IFC; see Swick et al. 2008).

To conclude, a pattern of differential genetic susceptibility was found for neural activation in the rFG. Although more clarity on the role of the FG during response inhibition is warranted. Our results indicate the importance of positive and negative social environments in behavioural and neural response inhibition. The findings extend previous research that thus far focused only on adversity. Before definite conclusions can be made as to how GxE interplay plays a role and which environmental influences are involved in inter-individual differences in response inhibition, replication of our findings in independent samples is necessary.

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## Statement of interest

In the past year, Dr. Faraone received income, travel expenses and/or research support from and/or has been on an Advisory Board for Pfizer, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA Pharma, Neurovance, Impax, NeuroLifeSciences and research support from the National Institutes of Health (NIH). His institution is seeking a patent



for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by: Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health* and Oxford University Press: *Schizophrenia: The Facts*. In the past 3 years, Dr. Buitelaar has been a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Shering Plough, UCB, Shire, Novartis and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. In the past 3 years, Dr. Hoekstra has been a consultant to/member of advisory board of Eli Lilly and Shire. Dr. Oosterlaan has received an unrestricted investigator initiated research grant from Shire. Dr. Franke received a speaker fee from Merck. Mr. van der Meer and Drs. Richards, van Rooij, Heslenfeld, Arias Vázquez and Hartman have no conflicts of interest to declare.

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